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WO 00/24391 A3

(54) Title: CONDUCTANCE OF IMPROPERLY FOLDED PROTEINS THROUGH THE SECRETORY PATHWAY

(57) Abstract: This invention provides the methodology and agents for treating disease or clinical condition which is at least partly the result of endoplasmic reticulum-associated retention of proteins. Thus, the methods and agents of the present invention provide for the release of normally retained proteins from the endoplasmic reticulum. The present invention is particularly useful for treating any disease or clinical condition which is at least partly the result of endoplasmic reticulum-associated retention or degradation of mis-assembled or mis-folded proteins. In particular, thapsigargin, cyclopiazonic acid, DBHQ or halothane can be used to allow the release of ΔF508CFTR or of a secretion-incompetent variant null (Hong Kong) of α_1-antitrypsin, in order to treat cystic fibrosis or chronic obstructive pulmonary disease (pulmonary emphysema) respectively.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 99/25221

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/343 A61K31/02 A61K31/407 A61K31/122
A61P11/00 A61P3/06 A61P5/48 A61P5/00 A61P7/00
A61P35/00 A61P31/12 G01N33/48 C12Q1/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 05810 A (2-03-95) 2 March 1995 (1995-03-02) see page 1 lines 7-19,24-30 page 2 page 5, line 18 - line 29 see page 6 lines 3-26, 35-38 see page 7, lines 6-7, 36-37 page 8 see page 9 lines 1-14, 26-37 page 10, line 1 - line 10 see example 5 page 20, lines 19-38 and page 21 --- -/--	5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2000	5.09.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GAC, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 99/25221

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 37878 A (GENZYME CORPORATION) 3 September 1998 (1998-09-03) abstract page 3 -page 5 page 9, line 18 page 11, line 30 - line 32 page 12, line 1 - line 11 page 13, line 11 - line 33 page 14 -page 18, line 8 page 18 -page 21	5
X	WO 93 13768 A (ARIAD PHARMACEUTICALS INC.) 22 July 1993 (1993-07-22) page 5, line 1 - line 13 page 11, line 30 - line 36 page 12 page 13, line 1 - line 24	5
X	US 5 674 898 A (CHENG S.H. ET AL.) 7 October 1997 (1997-10-07) column 2, line 55 - line 68 column 3, line 1 - line 2 column 6, line 46 see column 7 lines 1-4, 28-36 column 9, line 9 - line 55 column 24 -column 24; example 13 column 26, line 44 - line 54 see column 27 lines 20-25, 43-65 examples 16,17	5
Y	WAGNER ET AL.: "Molecular strategies for therapy of cystic fibrosis" ANN. REV. PHARMACOL. TOXICOL., vol. 35, 1995, pages 257-276, XP000905581 page 262	5,13
Y	BOUCHER R. C.: "Drug therapy in the 1990s: What can we expect for cystic fibrosis ?" DRUGS, vol. 43, no. 4, 1992, pages 431-439, XP000905268 page 434	5,13
A	TREIMAN M ET AL: "A tool coming of age: thapsigargin as an inhibitor of sarco-endoplasmic reticulum Ca-ATPases" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 19, no. 4, 1 April 1998 (1998-04-01), pages 131-135, XP004117812 ISSN: 0165-6147	5,13

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4

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/US 99/25221

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	YANG Y ET AL: "THE COMMON VARIANT OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR IS RECOGNIZED BY HSP70 AND DEGRADED IN A PRE-GOLGI NONLYSOSOMAL COMPARTMENT" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 90, no. 20, 15 October 1993 (1993-10-15), pages 9480-9484, XP002035737 ISSN: 0027-8424 ---	5,13
A	BARGON ET AL.: "Down-regulation of cystic fibrosis transmembrane conductance regulator gene expression by agents that modulate intracellular divalent cations" MOL. CELL. BIOL., vol. 12, no. 4, April 1992 (1992-04), pages 1872-1878, XP000905320 the whole document -----	5,13

4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/25221

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-16, 17-25 (as far as they concern an in-vivo method) and claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-4, 6-12,17-29,33
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

5,13,15,16,32 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 6-12,17-29,33

Present claims 1-4,6-12,17-29,33 relate to an extremely large number of possible compounds ("an agent") ,methods or diseases ("any disease or clinical condition"). In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.
Moreover the expression "or a derivative thereof" is indeterminate (Article 6 PCT).

Present claims 1-4,6-12,17-29,33 relate to compounds/methods or diseases defined by reference to a desirable characteristic or a pharmacological property, namely on the capacity of agents to release unduly retained proteins from the endoplasmic reticulum by acting at different levels/on different effectors in the cell.
The claims cover all compounds/methods/diseases having/using this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/methods/diseases. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound/method/disease by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently , the search is only possible for those parts of the claims which appear to be clear, supported and disclosed, namely on compounds of claims 13 and 14 and on diseases of claim 5 and the subjects of claims 30-32.

CONCLUSION:

Claims not searchable: claims 1-4,6-12,17-29,33
Claims partially searchable : 5,13-16
Claims completely searchable : 30-32

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 5,13,15,16,32 (all partially)

Use of thapsigargin in the treatment of cystic fibrosis and aerosol compositions containing it.

2. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of chronic obstructive pulmonary disease.

3. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of paroxysmal nocturnal hemoglobinuria.

4. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of familial hypercholesterolemia.

5. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of Tay-Sachs disease.

6. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of viral disease.

7. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of neoplastic diseases.

8. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of hereditary myeloperoxidase deficiency.

9. Claims: 5,13,15,16 (all partially)

Use of thapsigargin in the treatment of congenital insulin resistance.

10. Claims: 5,13,15,16,32 (all partially)

Use of clopiazonic acid in the treatment of cystic fibrosis and aerosol compositions containing it.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of chronic obstructive pulmonary disease.

12. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of paroxysmal nocturnal hemoglobinuria.

13. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of familial hypercholesterolemia.

14. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of Tay-Sachs disease.

15. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of viral diseases.

16. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of neoplastic diseases.

17. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of hereditary myeloperoxidase deficiency.

18. Claims: 5,13,15,16 (all partially)

Use of clopiazonic acid in the treatment of congenital insulin resistance.

19. Claims: 5,13,15,16,32 (all partially)

Use of DBHQ in the treatment of cystic fibrosis and aerosol compositions containing it.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

20. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of chronic obstructive pulmonary disease.

21. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of paroxysmal nocturnal hemoglobinuria.

22. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of familial hypercholesterolemia.

23. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of Tay-Sachs disease.

24. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of viral diseases.

25. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of neoplastic diseases.

26. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of hereditary myeloperoxidase deficiency.

27. Claims: 5,13,15,16 (all partially)

Use of DBHQ in the treatment of congenital insulin resistance.

28. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of cystic fibrosis.

29. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of chronic obstructive pulmonary disease.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

30. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of paroxysmal nocturnal hemoglobinuria.

31. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of familial hypercholesterolemia.

32. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of Tay-Sachs disease.

33. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of viral diseases.

34. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of neoplastic diseases.

35. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of hereditary myeloperoxidase deficiency.

36. Claims: 5,13,15,16 (all partially)

Use of halothane in the treatment of congenital insulin resistance.

37. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of cystic fibrosis.

38. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of chronic obstructive pulmonary disease.

39. Claims: 5,14-16 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of paroxysmal nocturnal hemoglobinemia.

40. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of familial hypercholesterolemia.

41. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of Tay-Sachs disease.

42. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of viral diseases.

43. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of neoplastic diseases.

44. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of hereditary myelopeoxidase deficiency.

45. Claims: 5,14-16 (all partially)

Use of antisense oligonucleotides to UGGT, calnexin or Ca2+-ATPase in the treatment of congenital insulin resistance.

46. Claim : 30

Method of screening candidate compounds to identify an agent that inhibits the endoplasmic reticulum-associated retention or degradation of mis-assembled or mis-folded proteins.

47. Claim : 31

Method of screening candidate compounds to identify an agent that inhibits the functional activity of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

UDP-glucose:glycosyl transferase.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/US 99/25221

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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